Section A-Research paper

QSAR and Quantum chemical study of sulfonamide derivatives with Carbonic Anhydrase (CA-II) Inhibitory Activity and its probabilistic Molecular Dynamic simulation approach

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Abstract: Initial geometry optimizations for all of the compounds were carried out using the molecular mechanics (MM) approach and the MM+ force fields in this study, which investigated QSAR on several bioactive sulfonamide compounds. The Density Functional Theory (DFT) method using Becke's three-parameter hybrid functional (B3LYP) and 6-31G (d) basis set enhanced the lowest energy conformations of the compounds generated by the MM method. The following parameters calculated from DFT calculations, such as molecular descriptors, dipole moment, electro negativity, total energy at 0 K, entropy at 298 K, HOMO and LUMO energies, provide important information and play a major role in the estimation of carbonic anhydrase (CA-II) inhibitory activity of the compounds. Several QSAR models were created using the multiple linear regression technique to calculate descriptors and carbonic anhydrase (CA-II) inhibitory data of the compounds. The statistically most significant of the above-mentioned QSAR models is a five-parameter linear equation with squared correlation coefficient R^2 values of about 0.7629 and adjusted correlation coefficient R^2_A values of around 0.6612. The carbonic anhydrase (CA-II) inhibitory activity was investigated in the context of regulatory variables. Computer-aided drug design is looking forward to a bright future thanks to Molecular Dynamic Simulation techniques for exploring the therapeutic potential of medicinal medicines and antibodies. Molecular dynamic stimulation can help to extend the work that has already been done.

Keywords: Carbonic Anhydrase (CA-II) inhibitors, DFT, HOMO, LUMO, Sulfonamides, QSAR, Molecular Dynamic Simulation.

Introduction

Carbonic acid anhydrase is zinc-holding enzymes generated in green plants and animals. They are dependable for interconversion of carbonic acid and carbon dioxide to bicarbonates and H_3O^+. Carbonic anhydrase II (CA II) catalyzes the regulating hydration of carbon dioxide through a two-step zinc hydroxide mechanism [1,2]

$$Zn - OH^- + CO_2 + H_2O \leftrightarrow Zn - H_2O + HCO_3^-$$

$$Zn - H_2O \leftrightarrow Zn - OH^- + H^+$$

They play an important role in numerous physico-pathological processes that contain the blood transport of CO_2, the formation of HCl in the stomach, and elevated pressure of the aqueous humor in the eyes (Glaucoma) [1-3]. Acetazolamide, methazolamide, dichlorphenamide, ethoxolamide, and dorzolamide, as carbonic anhydrase (CA-II) isozyme inhibitors, sulfonamide compounds are clinically used drugs for the treatment of glaucoma. When the enzyme is inhibited, the generation of carbonic acid (H_2CO_3) that usually dissociate into HCO_3^- and H_3O^+ is also inhibited. This results in the excretion of a large quantity of urine and ultimately dieresis [4]. Therefore, sulfonamides that inhibit carbonic anhydrase enzymes possess many applications as diuretic, anti-glaucoma, anti-epileptic, and anti-thyroid drugs. Present drugs which are used for the treatment of diseases like glaucoma, thyroid, and epileptic exhibit some side effect so the development of new drug agent is very important to reduce the side effect by creating a new agent for long term management of CA-II inhibitor.

Alteration in the existing drugs is one path to develop a new drug molecule for the above purpose, our research group members synthesized and reported new six sulfonamide derivatives by computational studies. These proposed derivatives have been achieved by alterationof sulfanilamide using the tail approach [5]. Table 1 displayed inhibition constants (KI) of these modified molecules against the carbonic anhydrase enzyme CA II. The value of KI shown in Table 1 is much lower than their mother molecule sulfanilamide. As a result, these compounds could be the focus of further research to see if they have the potential to become candidate medications.

Quantitative structure-activity relationships (QSAR) investigations are tools for estimating endpoints in organic compounds that act as medicines [6]. Molecules' physiological activity is determined by their composition and structure. Numerical representation of the molecular structures i.e., Molecular descriptors, are used to perform QSAR analysis [7]. Models of quantitative spectroscopic data activity relationship (QSDARs) show a link between a group of compounds' NMR spectra and their biological activities. Khadikar and co-workers described a different use of chemical shift of the $–SO_2NH_2$ protons as a molecular descriptor for modeling the carbonic anhydrase inhibition constant of benzene sulfonamides [8] but some recent QSAR studies [9-11] have presented that choice of the method DFT instead of semi-empiricalmethod results in better to the correlation between calculated results and experimental data. Therefore, the DFT method is anticipated to have an advantage to a statistically more accurate QSAR model

by comparing the semi-empirical methods. A path to dynamical properties of the system: transport coefficients, time-dependent responses to perturbations, rheological properties, and spectra are provided by Molecular Dynamics simulations.
PC simulations serve as a bridge between minute length and time scales and the research center's obviously apparent universe: they raise suspicions about particle cooperation and provide 'exact' mass property estimates. The forecasts are 'precise' as in they can be made as itemized as we like, subject to the restrictions forced by our PC financial plan. Simultaneously, the secret detail behind mass estimations can be uncovered. A model is a connection between the dissemination coefficient and speed autocorrelation work (the previous simple to quantify tentatively, the last a lot harder). Reenactments go about as an extension in another sense: among hypothesis and analysis [12].

The goal of this study is to use NMR chemical shifts of some benzene sulfonamides containing picolinoyl moieties to build a model carbonic anhydrase inhibition activity LogKi using QSAR and DFT methods. Because MD stimulation is important for drug design nowadays, our future work will focus on testing hypotheses by leading a reenactment using a similar model.

Material and Methods:

Theory and Computational details

The molecule used in this study, three-dimensional development and calculations were performed using the Gaussian 03 quantum chemistry package [13]. The optimization of the molecular structure of selected compounds was done using the functional hybrid B3LYP (Becke, three-parameter, Lee-Yang-Parr exchange-correlation function [14]. Density function theory (DFT) [15] method by utilizing Becke's three-parameter hybrid functional (B3LYP) formalism with electron basis set 6-31G for all atoms. The quantum chemical parameters obtained were E_{HOMO}, E_{LUMO}, Energy Difference (ΔE), Dipole Moment (μ), the total energy (TE), and Mulliken charge on heteroatom [16].

For designing of molecular descriptors from Gaussian03 output files Program CODESSA (**Co**mprehensive **De**scriptors for **S**tructural and **S**tatistical **A**nalysis), Version 2.7.2 was used [17]. Combination of calculated molecular descriptors with above-mentioned code uses diverse statistical structure-property activity correlation techniques for the study of investigational data.
For selecting the 'best' regression model, researchers used a heuristic method, implemented in CODESSA PRO.

In present years, the use of DFT method has been increased for calculating molecular properties of comparatively large molecules. With the help of DFT to analyze molecular properties such as optimized geometry and energy, with the accuracy as good as electron-correlated ab initio methods such as MP2, with requires much less computational time [18]. Accurate calculations of molecular properties are based on the selection of the basis set and method, and vary for the type of molecules of interest.

In many QSAR studies, molecular descriptors are considered in quantum mechanical methods. They provide molecular quantities that describe a molecule's reactivity, shape, and binding properties. Table 2 shows the results of the computations for the sulfonamide compounds mentioned above, as well as their experimental inhibition constants (KI).
Those descriptors which are associated with thermochemistry of molecules attained from frequency calculation at proper geometry, they are the total energy at 0 K (in a.u.) and entropy at 298 K (in cal/mol K). Energies (in eV) of the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) are recognized as quantum mechanical descriptors. This play a main role in managing many chemical reactions and shaping electronic band gaps in solids.The ionization potential and characterizes the susceptibility of a molecule is directly connected to the energy of the HOMO.

According to Koopmans theorem, the ionization potentialHOMO (eV) isdescribed as *HOMO* $I \square \square \square E$. Electron affinity calculation applies as per similar thought.The electron affinity and characterizes the susceptibility of the molecule towards attack by nucleophiles is directly related to the energy of the LUMO [19]. The electron affinity (eV) is achieved by Koopmans theorem as *LUMO A =E.*
The polarity of a molecule plays an important role for various physicochemical properties. The polarity of a molecule is explained by the most noticeable and most widely used quantity i.e., dipole moment.Table 3presented the remaining descriptors, namely electronegativity, is derived from the DFT framework.

In the future, we may be able to utilise MD stimulation to study molecular descriptors because, as Keretsu and colleagues indicated in 2020, Molecular Dynamic Simulations can help speed up the drug discovery process [20]. The researchers performed a molecular dynamics simulation study for COVID-19 main protease inhibitors. They evaluated commercially existing inhibitors against drug molecule targets of the virus. They observed 15 potential $3CL^{pro}$ inhibitors with higher binding affinity than that of a α-ketoamide inhibitor concluded by X-ray structure. Among them, they suggested that saquinavir and three other investigational drugs aclarubicin, TMC-310911, and faldaprevir as potential $3CL^{pro}$ inhibitors. Another Study by Saif et al., [21] investigated the many olives and turmeric compounds shows anti-viral drug potential that could be used as potential inhibitors against one of the target proteins of SARS-nCoV2 named Main protease (Mpro/3CLpro). In which researchers found that the best docking score given by Demethyloleoeuropein, Oleuropein, Rutin, Neuzhenide, Luteolin-7-rutinoside, Curcumin, and Tetrehydrocurcumin and form many stable complexes during simulation.

Their calculations suggested that these ligands had the possible inhibitory effects on Mpro of SARS-nCoV2, so, these herbal plants with no serious known side effects could help utilize COVID-19 infection as a home remedy. Peele et al., [22] aimed to develop asuitable anti-viral drug against the SARS-CoV-2 virus with the help of dynamic simulations using existing

powerful drugs from various virus treatments. They suggested an in-silico computational relationship between US-FDA-approved drugs, plant-derived natural drugs, and Coronavirus main protease (6LU7) protein. They screened 62 compounds and found the best docking score for lopinavir, amodiaquine, and theaflavin digallate (TFDG). Molecular dynamic (MD) simulation study was also achieved for 20 ns to prove the stability behavior of the main protease and inhibitor complexes. The stability of three compounds in the protein binding pocket as potent binders is supported by The MD simulation study.

Results and discussion

The value of the inhibition constants and chemical name of studies six sulfonamide compounds are taken from the literature [5], which shows in Table 1.

The specifics of structure studies are described in figure 1. Molecular descriptors, dipole moment, electro-negativity, total energy at 0 K, entropy at 298 K, HOMO, and LUMO energies achievedfrom DFT calculations are shown in Table 3. These descriptors are used to select the major parameters modifying the inhibitory activity of the compounds.

The multiple regression analysis was done by Data Analysis. For getting a good multi-parametric model we have carried out successive regression analysis and adopted the method of maximum R^2. Table 4 shows QSAR models. With the help of the squared correlation coefficient (R2), the *F*-test (F) and the standard deviation of the regression (Se) tested the goodness of fit of models.

The top models that were created are shown in Table 2. Between the models, the best goodness of fit is thePenta parametricmodel withthe R= 0.9402

Se = 0.4350 F=22.8646 Q= 2.1614

Balaban Index (J) is a highly discriminating index and with help of this index can be weighted easily yielding different types of Balaban indices. We have used J_{hetm} (Balaban type index from mass-weighted distance matrix), J_{hetv} (Balaban type index from Van der Waal's weighted distance matrix J_{hetp} (Balaban type index from polarizability weighted distance matrix), W (Weiner Index) and Chemical Shift. For developing some QSPR/QSAR models this index used successfully by Khadikar et al [23].

By Balaban and Balaban type indices with Chemical Shift were modeled log Ki using regression analysis and models showing good statistics were selected by NCSS software [24].

Model Validation

Cross-Validation is a practical and stable method for testing the impact of a model. The cross-validation parameters often used to be PRESS (Predicted residual sum of squares), SSY (sum of the squares of the response value), R^2_{cv} (Cross validated R^2 or overall predictive ability), PSE (predictive square error), and PE (Probable error of the coefficient of correlation.

HOMO – LUMO

The electron-donating ability of the molecule is correlated with E_{HOMO} is a quantum chemical parameter.When the lower the E_{HOMO}, the weaker the donating electron ability, indicating that the electrophilic reaction happens more easily and the inhibitory activity of the molecules is elevated.

Figures show that all molecules may have different HOMO and LUMO distributions. The HOMO densities were largely found on the entire moiety and strongly distributed in all regions, while the LUMO densities were concentrated in the same region. Figures show the optimized structures and HOMO and LUMO densities of all molecules.

Energy gap (ΔE)

For a function of reactivity of a molecule, ΔE (*energy gap* $\Delta E = E_{LUMO} - E_{HOMO}$) is an important parameter. The magnitude of lower value of ΔE reduces the reactivity of the molecule increases leading to better inhibition efficiency and elimination of an electron from the last occupied orbital will be down.

The term soft molecule is used for those molecules which have a low energy gap, and are easily polarizable and is generally coupled with high chemical activity and low kinetic stability. In general, the electron transfer mechanism is improved when the energy gap is reduced.

Dipole moment (μ)

The applied Dipole moment can be used to discuss the inhibitors' molecular structure and the measure of polarity of a polar covalent bond. The dipole moment values for the molecules investigated in this study are higher than that of H_2O (=1.85 D). These chemicals' high dipole moment values could indicate significant dipole–dipole interactions.

Ionization potential (I)

High ionization energy indicates chemical inertness and consistency. The values of (I) are listed in the table, and the low ionization energy indicates a larger inhibitory action of the chemical in the result.

Global hardness (η) and Softness (σ)

A big energy gap can be seen in a hard molecule, while a tiny energy gap can be seen in a soft molecule. For all molecules, the chemical hardness (η) and softness (σ) values were taken into account. The stronger the molecular stability and reactivity, the lower is the value of global hardness (η).

Total energy (TE)

The total energy (TE) is a crucial metric. The sum of a system's internal, potential, and kinetic energy is its total energy. The calculations reveal that the lower the total energy, the more stable the molecules are. The compound's chemical stability is linked to its low total energy. As a result, inhibitory action varies inversely with molecule total energy.

Conclusions

With the help of the above discussion, it is specified that the DFT-based quantum mechanical molecular descriptors may be used for QSAR modeling of inhibition constant (Log*K*I) of sulfonamides compounds to CA-II isozyme. The most excellent designed model is a penta-parametric regression equation with a very fine statistical fit and good analytical power as evident from its R= 0.9402 Se = 0.4350 F=22.8646 Q= 2.1614values. A study shows that descriptors used in the models designate that inhibition of CA-II is influenced by energy, entropy, polarity, and reactivity indexes of sulfonamide compounds.

MD simulation is upcoming equipment that is used in the area of drug design such as Thakral et al., [25] performed molecular dynamic simulation studies of 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-N-(alkyl/aryl)-4-nitrobenzamide derivatives as potent antidiabetic agents. Their group performed molecular dynamic simulations for validating compound's α-glucosidase and α-amylase inhibitory potential, RMSD analysis of ligand-protein complex recommended the stability of the highest active compound 50 in the binding site of target proteins. Another study done by Mohammad Ajmal Ali [26] found that the compound '3,5,7,3′,5′-pentahydroxy-flavanonol-3-O-α-L-rhamnopyranoside' reported from Bauhinia strychnifoliaCraib (family Fabaceae) have ten times more cytotoxicity against certain cancer cell line than the anti-cancer drugs, but minimum side effect such as nontoxic to normal cells. They studied its stability with molecular dynamics simulation.

Thus, from various studies and approaches it is evident that Molecular docking and molecular mechanics simulations are critical methodologies in achieving a coherent drug design or a chemical process modeling. It dives to deep atomic experiences as designs and systems assisting analysts with portraying different compliances and sub-atomic communications as far as energy and restricting affinities, giving the likelihood to look among handfuls, many genuine or fanciful mixtures, the most reasonable for an exact, obvious reason. Beginning from a recognized substance with a known instrument of activity and organic movement, we can envision other related mixtures as medication up-and-comers with better adequacy and fewer results. These in-silico strategies assist us with distinguishing and choice among huge compound libraries the most appropriate remedial specialist before beginning its substance union. That can be called virtual science before the response tube. It is extremely helpful, decreasing the utilization of substance reagents, preclinical, clinical preliminaries, and time [27].

Computational techniques, applied at the beginning phases of the medication configuration measure, utilize current innovation to give significant experiences into the comprehension of substance frameworks in a virtual way, supplementing test investigation. Molecular docking is an in-silico technique utilized to anticipate restricting methods of macromolecules in proximity with a receptor and to anticipate their atomic interactions. Additionally, the philosophy opens up the chance of positioning these mixtures as indicated by a progression decided to utilize specific scoring capacities. Docking conventions relegate numerous approximations, and the greater part of them requires receptor adaptability. Hence, the dependability of the subsequent protein-ligand buildings is questionable. Although MD techniques are expensive in combination with molecular docking they are significantly complimenting. MD reproductions can be utilized before docking since a progression of "new" and more extensive protein conformities can be removed from the handling of the subsequent direction and utilized as focuses for docking. They additionally can be used deduced to enhance the constructions of the last edifices from docking, compute more itemized cooperation energies, and give data about the ligand restricting instrument. Here, we center on conventions that suggest the docking-MD mix as an intelligent way to deal with further developing the medication disclosure measure [28].

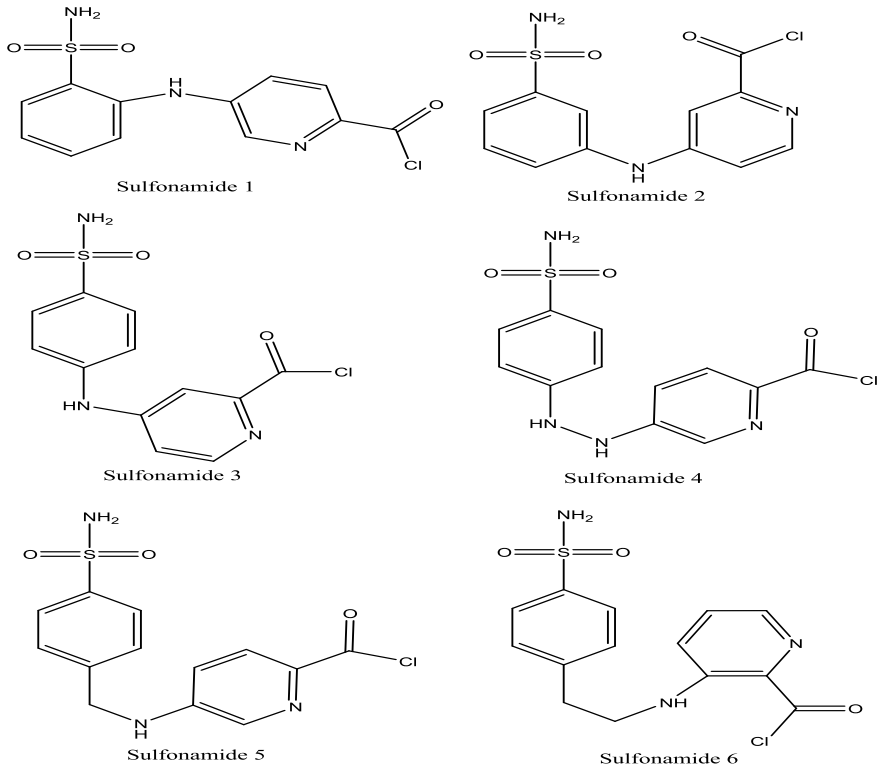


Figure 1 : Structural details of selected molecules

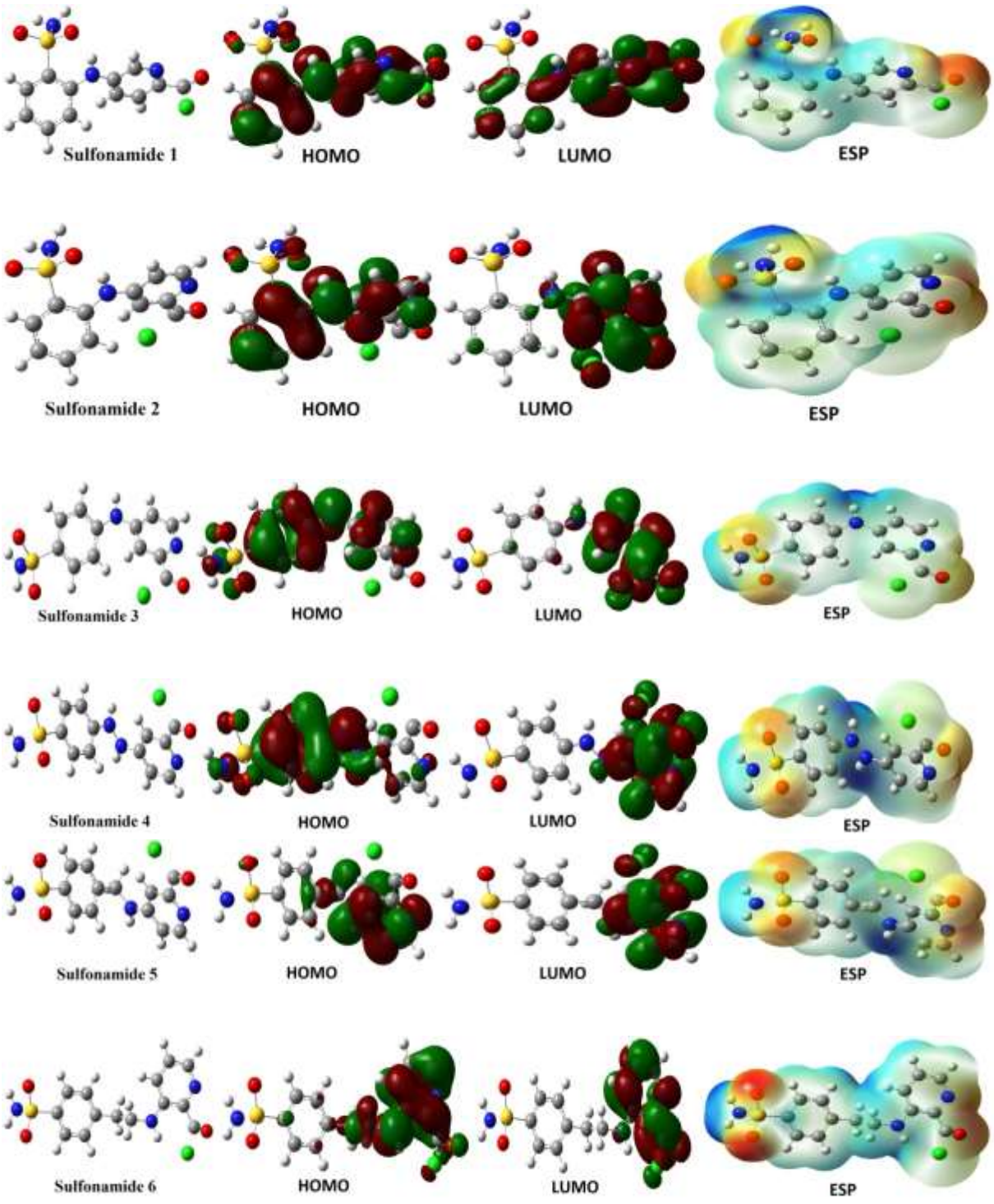


Figure 2: Energy Profile of studies Sulfonamide

Table 1. The list of chemical name of the compounds studied and their observed Log*K*I values.

Comp. No.	logKi	Calcu. logKi	Residual
1	4.33	4.039502	0.290498
2	4.29	3.711672	0.578328
3	4.17	3.813534	0.356466
4	4.35	3.732119	0.617881
5	3.04	3.686516	-0.64652
6	3.04	3.574363	-0.53436

1. 4-{[(4-sulfamoylphenyl) methyl]amino}pyridine-2-carbonyl chloride
2. 5-{[(2-sulfamoylanilinol) methyl]pyridine-2-carbonyl chloride
3. 4-{[(3-sulfamoylanilino) methyl]pyridine-2-carbonyl chloride
4. 4-{[(4-sulfamoylanilino) methyl]pyridine-2-carbonyl chloride
5. 4-{[2-(4-sulfamoylphenyl) hydrazinly}pyridine-2-carbonyl chloride
6. 43{[2-(4-sulfamoylphenyl)ethyl]amino}pyridine-2-carbonyl chloride

Table 2. Calculated descriptors, predicted and experimental inhibitory activity data of compounds studied

Comp. No.	J	Jhetm	Jhetz	Jhetp	W	logKi	Calcu. logKi
1	1.811	2.697	2.697	1.316	865	4.33	4.039502
2	1.725	2.564	2.564	1.285	905	4.29	3.711672
3	1.652	2.453	2.453	1.257	945	4.17	3.813534
4	1.591	2.335	2.336	1.098	1126	4.35	3.732119
5	1.591	2.243	2.243	1.237	1126	3.04	3.686516
6	1.539	2.082	2.082	1.220	1328	3.04	3.574363

Table 3: .Calculated descriptors, predicted and experimental inhibitory activity data of compounds studied.

compound	E_{HOMO}(eV)	E_{LUMO}(eV)	ΔE	dipol	Total Energy(Ev)	η	σ	I
Sulfonamide 1	-6,56834	-2,55218	4,01616	8,5444	-46558,04297	2,00808	0,49799	6,56834
Sulfonamide 2	-6,54629	-2,64143	3,90486	3,9791	-46558,03214	1,95243	0,51218	6,54629
Sulfonamide 3	-6,72780	-2,77477	3,95303	9,4060	-46557,90553	1,97651	0,50594	6,72780
Sulfonamide 4	-6,73895	-2,65259	4,08637	11,1829	-48062,42931	2,04318	0,48943	6,73895
Sulfonamide 5	-6,79365	-2,50347	4,29018	11,7335	-47626,63674	2,14509	0,46618	6,79365
Sulfonamide 6	6,53378	-2,50211	-9,03588	5,3424	-48695,36367	-4,51794	-0,22134	-6,53378

Table 4.: Obtained QSAR models for the molecules studied against CA-II isozyme.

Model 1.

$$\text{Log Ki} = -4.3477 + 13.4524J + 475.2729J_{hetz} - 480.1132J_{hetm} - 2.3101J_{hetv}$$

N=6, R=0.7977,Se= 0.7461,F=7.0015, Q= 1.0692

Model 2.

$$\text{LogKi} = -22.7814 - 0.0068W + 4.2621\,{}^{0}x - 6.4103\,{}^{2}x - 1.7479\,\text{ȝ} - 2.4919\,{}^{5}x^{v} - 2.1201\,{}^{2}x^{v} - 1.8547\,{}^{3}x$$

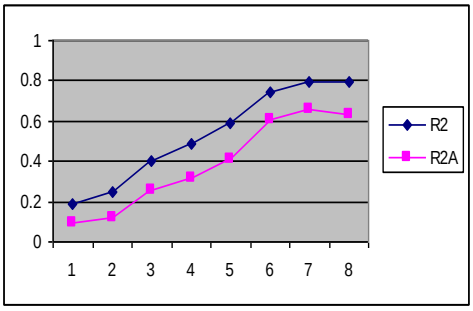
N=6, R=0.8990,Se= 0.6009,F=7.8343, Q= 1.4961

Model3

$$\text{Log Ki} = -9.5870 - 0.0018W + 1.0489\text{ȝ} - 5.4459J_{hetm} + 14.3929J - 2.3658J_{hetp}$$

N=6, R=0.9402,Se= 0.4350,F=22.8646, Q= 2.1614

Figure. 4: Modeling logKi using Balaban and Balaban type indices



Acknowledgement: Authors are grateful to Dr KN Guruprasad, Director, SVIS, Indore for providing the necessary facilities. Special thanks are due to Honorable Vice-Chancellor Dr Upinder Dhar, SVVV, Indore for encouragement. Appreciation to Dr. Jeetendra Bhawsar of Medicaps University in Indore for his help with the DFT technique. The authors also acknowledge the motivation by Dr. Archana Keerti Chowdhary, Principal, IPS Academy, Institute of Engineering and Science, Indore for carrying out the research work.

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